Amendments to the Claims

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (Original) An isolated antibody capable of binding to human tissue factor, wherein said antibody does not inhibit tissue factor mediated blood coagulation compared to a normal plasma control and can initiate an Fc-mediated mechanism.

2. (Original) The antibody of claim 1, wherein said Fc-mediated mechanism comprises the ability to initiate antibody-dependent cell-mediated cytotoxicity (ADCC).

3. (Original) The antibody of claim 1, wherein said Fc-mediated mechanism comprises the ability to initiate complement-dependent cytotoxicity (CDC).

4. (Original) The antibody of claim 1, wherein said antibody is selected from the group consisting of: a monoclonal antibody, chimeric antibody, single chain antibody, humanized antibody and antibody product of a Fab expression library.

5. (Original) The antibody of claim 1, wherein said antibody is a modified antibody.

6. (Original) The antibody of claim 1, wherein said antibody is conjugated to a cytotoxic agent.

7. (Original) The antibody of claim 6, wherein said cytotoxic agent is selected from the group consisting of: a paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoid, procaine, tetracaine, lidocaine, propranolol, puromycin, and a radioisotope.

8. (Original) The antibody of claim 1, wherein said antibody is conjugated to a detectable agent.

9. (Original) The antibody of claim 8, wherein said detectable agent is selected from the group consisting of: an enzyme, prosthetic group, fluorescent material, luminescent material, bioluminescent material, radioactive material, positron emitting metal using a positron emission tomography, and nonradioactive paramagnetic metal ion.

10. (Original) An immunoglobulin molecule comprising the heavy or light chain variable region of the antibody of claim 1.

11. (Original) An isolated anti-antibody capable of interfering with the binding of the antibody of claim 1 to human tissue factor.

12. (Original) A monoclonal antibody that binds to the same epitope as a monoclonal antibody produced by a hybridoma cell line TF196 deposited under ATCC Accession No. PTA-5196.

13. (Original) A monoclonal antibody that binds to the same epitope as a monoclonal antibody produced by a hybridoma cell line TF260 deposited under ATCC Accession No. PTA-5197.

14. (Original) A monoclonal antibody that competes for binding to the same epitope as a monoclonal antibody produced by a hybridoma cell line TF196 deposited under ATCC Accession No. PTA-5196 or a monoclonal antibody produced by a hybridoma cell line TF260 deposited under ATCC Accession No. PTA-5197.

15. (Original) An antibody obtainable from a hybridoma cell line TF196 deposited under ATCC Accession No. PTA-5196 or TF TF260 deposited under ATCC Accession No. PTA-5197.

16. (Original) A hybridoma capable of producing an antibody having the binding characteristics of an antibody obtained from a hybridoma cell line TF196 deposited under ATCC Accession No. PTA 5196.

17. (Original) The hybridoma of claim 16, which is the hybridoma cell line TF196 deposited under ATCC Accession No. PTA-5196.

18. (Original) A hybridoma capable of producing an antibody having the binding characteristics of an antibody obtained from a hybridoma cell line TF260 deposited under ATCC Accession No. PTA-5197.

19. (Original) The hybridoma of claim 18, which is the hybridoma cell line TF260 deposited under ATCC Accession No. PTA-5197.

20. (Original) A monoclonal antibody that competes for binding to the same epitope as a monoclonal antibody produced by a hybridoma cell line TF278 deposited under ATCC Accession No. PTA-5676 or a monoclonal antibody produced by a hybridoma cell line TF392 deposited under ATCC Accession No. PTA-5677 or a hybridoma cell line TF9 deposited under ATCC Accession No. PTA-5674.

21. (Original) An antibody obtainable from a hybridoma cell line TF278 deposited under ATCC Accession No. PTA-5676 or a hybridoma cell line TF392 deposited under ATCC Accession No. PTA-5677 or a hybridoma cell line TF9 deposited under ATCC Accession No. PTA-5674.

22. (Original) A hybridoma capable of producing an antibody having the binding characteristics of an antibody obtained from a hybridoma cell line TF278 deposited under ATCC Accession No. PTA 5676.

23. (Original) The hybridoma of claim 22, which is the hybridoma cell line TF278 deposited under ATCC Accession No. PTA-5676.

24. (Original) A hybridoma capable of producing an antibody having the binding characteristics of an antibody obtained from a hybridoma cell line TF392 deposited under ATCC Accession No. PTA-5677.

25. (Original) The hybridoma of claim 24, which is the hybridoma cell line TF392 deposited under ATCC Accession No. PTA-5677.

26. (Original) A hybridoma capable of producing an antibody having the binding characteristics of an antibody obtained from a hybridoma cell line TF9 deposited under ATCC Accession No. PTA-5674.

27. (Original) The hybridoma of claim 26, which is the hybridoma cell line TF9 deposited under ATCC Accession No. PTA-5674.

28. (Original) A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 1 and a pharmaceutically acceptable carrier.

29. (Original) A method of treating cancer in a patient, said method comprising administering to said patient the pharmaceutical composition of claim 28.

30. (Original) The method of claim 29, wherein said cancer is a solid tumor.

31. (Original) The method of claim 29, wherein said cancer is selected from the group consisting of non-small cell lung cancer, breast cancer, colon cancer and prostate cancer.

32. (Original) The method of claim 29, wherein said pharmaceutical composition comprises an antibody conjugated to a cytotoxic agent.

33. (Original) A method of detecting cancer, said method comprising providing the antibody of claim 8 to a sample or subject and detecting the binding of said detectable agent to a cancer cell.

34. (Original) The method of claim 33, wherein said cancer is selected from the group consisting of non-small cell lung cancer, breast cancer, colon cancer and prostate cancer.

35. (Original) A method of producing a monoclonal antibody capable of binding to tissue factor, wherein said antibody does not inhibit tissue factor mediated blood coagulation compared to a normal plasma control, and wherein said antibody can initiate an Fc-mediated mechanism, said method comprising:

(a) immunizing a mammal with a purified extracellular domain of human tissue factor;

(b) preparing a cell suspension from lymph nodes of said immunized mammal;

(c) fusing cells from the cell suspension of (b) with myeloma cells; and

(d) identifying a clone from a hybridoma generated from the fusion in (c), wherein said clone produces an antibody capable of binding to human tissue factor and does not inhibit tissue factor mediated blood coagulation compared to a normal plasma control and wherein said antibody can initiate an Fc-mediated mechanism.

36. (Original) An antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:6, 8, 10 and 12.

37. (Original) An antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:19, 21, 23, 25, 27, 29 and 31.

38. (Original) An isolated nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence selected from the group consisting of SEQ ID NOs:6, 8, 10 and 12.

39. (Original) An isolated nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence selected from the group consisting of SEQ ID NOs:19, 21, 23, 25, 27, 29 and 31.

40. (Original) An isolated polynucleotide encoding an antibody comprising an amino acid sequence selected from the group consisting of:

(a) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF196;

(b) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF260;

(c) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF196;

(d) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF260;

(e) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF196;

(f) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF260;

(g) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF196;

(h) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF260;

(i) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF196;

(j) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF260;

(k) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF196; and

(l) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF260.

41. (Original) An isolated polynucleotide encoding an antibody comprising an amino acid sequence selected from the group consisting of:

(a) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF278;

(b) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF392;

(c) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF9;

(d) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF278;

(e) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF392;

(f) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF9;

(g) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF278;

(h) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF392;

(i) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF9;

(j) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF278;

(k) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF392;

(l) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF9;

(m) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF278;

(n) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF392;

(o) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF9;

(p) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF278;

(q) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF392; and

(r) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF9.

42. (Original) An isolated nucleic acid molecule comprising a polynucleotide capable of hybridizing under stringent conditions to the complement of SEQ ID NO:5, 7, 9 or 11, and which encodes a polypeptide that can bind to human tissue factor without inhibiting tissue factor mediated blood coagulation compared to a normal plasma control, and which can initiate an Fc-mediated mechanism.

43. (Original) An isolated nucleic acid molecule comprising a polynucleotide capable of hybridizing under stringent conditions to the complement of SEQ ID NO:18, 20, 22, 24, 26, 28 or 30, and which encodes a polypeptide that can bind to human tissue factor without inhibiting tissue factor mediated blood coagulation compared to a normal plasma control, and which can initiate an Fc-mediated mechanism.

44. (Original) A vector comprising the isolated polynucleotide of claim 40.

45. (Original) A vector comprising the isolated polynucleotide of claim 41.

46. (Original) A host cell comprising the vector of claim 44.

47. (Original) A host cell comprising the vector of claim 45.

48. (Original) A host cell genetically engineered to comprise the isolated polynucleotide of claim 40.

49. (Original) A host cell genetically engineered to comprise the isolated polynucleotide of claim 41.

50. (Original) A method of making an antibody comprising:

(a) expressing the antibody encoded by the isolated polynucleotide of claim 40; and

recovering said antibody.

51. (Original) A method of making an antibody comprising:

(a) expressing the antibody encoded by the isolated polynucleotide of claim 41; and

(b) recovering said antibody.

52. (Original) An isolated polypeptide comprising an amino acid sequence having at least 95% sequence identity to an amino acid sequence selected from the group consisting of:

(a) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF196;

(b) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF260;

(c) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF196;

(d) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF260;

(e) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF196;

(f) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF260;

(g) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF196;

(h) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF260;

(i) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF196;

(j) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF260;

(k) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF196; and

(l) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF260;

which polypeptide can bind to human tissue factor without inhibiting tissue factor mediated blood coagulation compared to a normal plasma control and which can initiate an Fc-mediated mechanism.

53. (Original) An isolated polypeptide comprising an amino acid sequence having at least 70% sequence identity to an amino acid sequence selected from the group consisting of:

(a) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF278;

(b) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF392;

(c) at least one CDR region of a VH domain of the antibody expressed by hybridoma cell line TF9;

(d) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF278;

(e) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF392;

(f) at least two CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF9;

(g) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF278;

(h) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF392;

(i) at least three CDR regions of a VH domain of the antibody expressed by hybridoma cell line TF9;

(j) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF278;

(k) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF392;

(l) at least one CDR region of a VL domain of the antibody expressed by hybridoma cell line TF9;

(m) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF278;

(n) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF392;

(o) at least two CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF9;

(p) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF278;

(q) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF392; and

(r) at least three CDR regions of a VL domain of the antibody expressed by hybridoma cell line TF9;

which polypeptide can bind to human tissue factor without inhibiting tissue factor mediated blood coagulation compared to a normal plasma control and which can initiate an Fc-mediated mechanism.

54. (Original) A kit comprising the pharmaceutical composition of claim 28.

55. (Original) The kit of claim 54, further comprising printed instructions for its use.

56. (Original) The kit of claim 54, further comprising a printed matter describing the use of the composition to treat cancer, a pre-recorded media device describing the use of the composition to treat cancer, or a planner.

57. (Original) The kit of claim 56, wherein said printed matter is a book, booklet, brochure or leaflet.

58. (Original) The kit of claim 56, wherein said pre-recorded media device a DVD, a videotape cassette, a CD-ROM, an audiocassette, or an audio compact disk.

59. (Original) A kit comprising a pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 36.

60. (Original) The kit of claim 59, further comprising printed instructions for its use.

61. (Original) A kit comprising a pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 37.

62. (Original) The kit of claim 61, further comprising printed instructions for its use.

63. (Original) A method of delivering the pharmaceutical composition of claim 28 to a patient in need thereof, said method comprising:

(a) registering in a computer readable storage medium identity of a physician permitted to prescribe said pharmaceutical composition;

(b) providing said patient with counseling information concerning a risk attendant to said pharmaceutical composition;

(c) obtaining informed consent of said patient to receive said pharmaceutical composition despite said risk;

(d) registering said patient in the computer readable medium after obtaining said informed consent; and

(e) permitting said patient access to said pharmaceutical composition.

64. (Original) The method of claim 63, wherein said access to said pharmaceutical composition is a prescription.

65. (Original) A method of educating a consumer regarding the pharmaceutical composition of claim 28, said method comprising distributing said pharmaceutical composition to a consumer with consumer information at a point of sale.

66. (Original) The method of claim 65, wherein said consumer information is presented in a format selected from the group consisting of: English language text, a

foreign language text, a visual image, a chart, a telephone recording, a website, and access to a live customer service representative.

67. (Original) The method of claim 65, wherein said consumer information is a direction for use, appropriate age.use, indication, contraindication, appropriate dosing, warning, telephone number or website address.

68. (Original) The method of claim 65, further comprising providing professional information to a relevant person in a position to answer a consumer question regarding said pharmaceutical composition.

69. (Original) The method of 68, wherein said relevant person is a physician, physician assistant, nurse practitioner, pharmacist or customer service representative.

70. (Original) The method of claim 65, wherein said distributing is to a location with a pharmacist or a health care provider.

71. (Original) A method of identifying a pharmaceutical composition of claim 28, and commercializing the same as a drug, said method comprising:

(a) isolating an antibody capable of binding to human tissue factor, wherein said antibody does not inhibit tissue factor mediated blood coagulation compared to a normal plasma control and can initiate an Fc-mediated mechanism;

(b) repeating (a) to obtain a plurality of candidate antibodies that may prove therapeutically effective;

(c) demonstrating for at least one such candidate antibody its non-toxic nature when administered to a non-human animal;

(d) conducting a supervised clinical trial to demonstrate non-toxic and effective character of the candidate antibody of (c);

(e) securing approval of a regulatory agency to distribute said the candidate antibody of (d) to treat cancer; and

(f) making a pharmaceutical composition comprising the candidate antibody of (e) as an active agent.

72. (Original) The method of claim 71, wherein said cancer is selected from the group consisting of non-small cell lung cancer, breast cancer, colon cancer and prostate cancer.

73. (New) An isolated antibody capable of binding to human tissue factor, wherein said antibody does not inhibit tissue factor compared to normal plasma control and is conjugated to a cytotoxic agent or a detectable agent.

74. (New) The antibody of claim 73, wherein said antibody is selected from the group consisting of: a monoclonal antibody, chimeric antibody, single chain antibody, humanized antibody and antibody product of a Fab expression library.

75. (New) The antibody of claim 73, wherein said cytotoxic agent is selected from the group consisting of: a paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin,

doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoid, procaine, tetracaine, lidocaine, propranolol, puromycin, and a radioisotope.

76. (New) The antibody of claim 73, wherein said detectable agent is selected from the group consisting of: an enzyme, prosthetic group, fluorescent material, luminescent material, bioluminescent material, radioactive material, positron emitting metal using a positron emission tomography, and nonradioactive paramagnetic metal ion.

77. (New) A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 73 and a pharmaceutically acceptable carrier.

78. (New) A method of treating cancer in a patient, said method comprising administering to said patient the pharmaceutical composition of claim 77.

79. (New) The method of claim 78, wherein said cancer is a solid tumor.

80. (New) The method of claim 78, wherein said cancer is selected from the group consisting of non-small cell lung cancer, breast cancer, colon cancer and prostate cancer.

81. (New) A kit comprising the pharmaceutical composition of claim 77.